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EXAMINER

RONALD R SANTUCCI
PITNEY HARDIN KIPP & SZUCH
711 THIRD AVENUE
20TH FLOOR
NEW YORK NY 10017

SOLAYA, J

ART UNIT	PAPER NUMBER
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1655

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/485,434

Applicant(s)

Berghof et al

Examiner
Jehanne Souaya

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Jun 14, 2001

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 7 and 9-27 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 7 and 9-27 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) Notice of References Cited (PTO-892) 18) Interview Summary (PTO-413) Paper No(s). _____

16) Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) Notice of Informal Patent Application (PTO-152)

17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 20) Other: _____

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DETAILED ACTION

1. Currently, claims 7, 9-21 and newly added claims 22-27 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON- FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Nucleotide Sequences

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because the specification lists nucleic acid sequences which do not have SEQ ID NO identifiers.

Maintained Rejections

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 7, 9-21, and newly added claims 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is is indefinite with regard to the phrase “or nucleic acid molecule that can be used for such a set” as it is unclear how the nucleic acid molecule ‘can be used’ with regard to the set in the preamble of the claim. Furthermore, the claim is indefinite in the recitation of “the sequence region comprising or being a phylogenetically conserved base sequence” as it is unclear whether “the sequence region” refers to one or more than one nucleic acid.

Claim 9 as written is unclear with regard to the phrase “in respect of its sequence”. The claim should read --*with respect to its sequence*--.

Claims 12 and 23 are indefinite in the recitation of “where appropriate” because it is unclear what is considered “appropriate” for modification. Neither the claim nor the specification make clear the metes and bounds of claim.

Claim 13 is indefinite in the recitation of “have been replaced by analogous building blocks known per se as probes or primers” as it is unclear if the 1 or 2 nucleotides have been replaced by probes or primers. It is further unclear what is meant by the term analogous building blocks as it is unclear what the claim considers “analogous” to the nucleotides that are being replaced.

Claim 14 is indefinite with respect to the term “nucleic acid-like” as it is unclear what characteristics the modified groups can possess such that they remain “nucleic-acid-like”.

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Claim 18 is indefinite as it does not contain any positive active process steps nor does it contain a positive process step relating back to the preamble. The claim merely states a use for an oligonucleotide but does not include any active steps for such use. *does not teach how*

Claim 19 is indefinite because it is unclear where the steps of nucleic acid hybridization, nucleic acid amplification, or both are carried out in the method.

Claim Rejections - 35 USC § 103

5. Claims 7 and 9-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holmes et al (WO95/00664).

The claims are drawn to isolated nucleic acid molecules that can distinguish between the following *Salmonella enterica* subspecies: *enterica*, *salamae*, *arizonae*, *diarizonae*, *houtenai*, *bongori*, and *indica*. The nucleic acid molecules are characterized in that the sequences of each subspecies have been aligned to determine regions of similarity and variability to design primers and probes that universally hybridize to a number of subspecies and specifically hybridize to a certain subspecies and not to other subspecies, thereby identifying nucleic acid samples as containing *Salmonella enterica* and further distinguishing each subspecies through PCR amplification or hybridization.

Holmes teaches an invention which provides nucleic acid molecules for the detection and identification of *Salmonella* species, and for detecting one or more *Salmonella* serotypes and to kits comprising these nucleic acid molecules (see abstract). Holmes teaches a need for detecting

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Salmonella because the incidence of salmonellosis has increased significantly during the last two decades in western countries and that while standard culture methods are still widely used for detection of *Salmonella* in foods, the control of infection depends on the availability of rapid and precise tests for monitoring of primary animal production (see p. 1). Holmes teaches that nucleic acid based methods for detection of a DNA or RNA from a target organism have proliferated and that the invention of Holmes is based on using certain fragments of the *Salmonella typhimurium* LT2 chromosome (or corresponding nucleic acid fragments having the same sequence of bases, including RNA, PNA, etc) as primers in PCR and other amplification systems, in particular certain fragments corresponding to regions of the genome which are highly conserved in *Salmonella* species (see paragraph bridging pages 2 and 3). Holmes further teaches that fragments to conserved regions are useful in detecting and identifying *Salmonella* species generally, while fragments from less conserved regions are useful for identifying infections from different serotypes of *Salmonella* (see p. 3). Holmes teaches using 146 *Salmonella* strains (table 2) and 82 non *Salmonella Enterobacteriaceae* strains (table 3). Holmes further teaches that 8 oligonucleotide sequences were selected from the sequence and tested for their ability to discriminate between *Salmonella* and non *Salmonella* bacteria and teaches various results in the primer pairs ability to identify and distinguish *Salmonella* from non *Salmonella* bacteria and from different serotypes of *Salmonella* (see p. 14, 15, and table 1,2 and 3, examples 1 and 2). Holmes specifically teaches evaluation of a *Salmonella* specific PCR assay and the detection of *enterica*, *salamae*, *arizona*, *diarizona*, *houtenai*, *bongori*, and *indica* and teaches application of the

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general method in the detection of *Salmonella* in pork and beef (example 3). Holmes teaches kits containing these nucleic acid primers and probes for use in the method taught by Holmes. It is also noted that the sequences of SEQ ID NOS 1, 3, 6, and 9 are found in SEQ ID NO 1, taught by Holmes.

Although Holmes does not teach the exact nucleic acid molecules "consisting" of the SEQ ID Nos taught in claim 8, Holmes provide motivation for the skilled artisan to construct the sequences of claim 8 and the sequences encompassed by the broadly claimed invention. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct sequences as Holmes teaches how to construct nucleic acid molecules for the purpose of detecting different serotypes of *Salmonella*. The ordinary artisan would have been motivated to construct such nucleic acid molecules as Holmes teaches a need for the detection and differentiation of *Salmonella* for the purposes of controlling infection caused by *Salmonella*.

It should be noted that the state of the art was very high at the time the invention was filed to construct probes and primers for the detection and differentiation of different strains of closely related bacteria and fungi. For example, a number of US patents were given to Hogan et al (5,714,321 is enclosed) to methods and nucleic acids for detecting and differentiating different strains of bacteria. A large number of references were available, at the time the invention was made, that taught the ordinary artisan how to align sequences of bacteria to determine regions of similarity and variability to detect and differentiate different strains of bacteria. As the strains and subspecies of the bacteria were known and available in the art at the time of filing, it would have

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been *prima facie* obvious to one of ordinary skill to align the sequences of different subspecies of *Salmonella* for the purpose of providing nucleic acids for detecting and differentiating different subspecies of *Salmonella*. A showing of unexpected results, however, could overcome this rejection. Evidence that certain primers or probes worked better than others would constitute unexpected results, and therefore, those *specific* probes and primers would be patentable over the disclosure of Holmes and the general high state of the art.

Response to Arguments

The response traverses that Holmes teaches false negative results and that therefore, the ordinary artisan would not be motivated to use the disclosure of Holmes to arrive at the instantly claimed invention. This argument has been thoroughly reviewed but was found unpersuasive because Holmes does teach successful detection of all subspecies of table 2, albeit with different combinations of primers. However, the claims of the instant invention are not drawn to specific primer combinations or the stipulation that a single nucleic acid will function to detect all subspecies without false positive or false negative results. Four of the nucleic acid probes and primers of the instant invention are taught in the disclosure of Holmes. Furthermore, Holmes provides motivation and a reasonable expectation of success that probes and primers to this region will detect different *Salmonella* serotypes. While Holmes does not teach the specific sequences consisting of SEQ ID NOS 1, 3, 6, and 9, Holmes does teach how to align the region of different serotypes of *Salmonella* to determine regions of similarity and differences in a method

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of detection. Therefore, the ordinary artisan would have considered probes and primers to this region as equivalent in a method of detecting different serotypes of *Salmonella* such that a number of specific serotypes (as claimed in claim 7) would be detected.

This rejection could be overcome with a showing of unexpected results over the disclosure of Holmes. IE: specific probe and primer combinations achieved 100% detection of all strains in claim 7. The specification and the declaration have been thoroughly reviewed. Firstly, it cannot be determined from the recitation in the specification as to which primer and probe combinations achieved 100% detection of the claimed Serotypes. The specification teaches using primers and probes Sa1-Sa10, however the specification does not define which nucleic acid sequences these are drawn to. Furthermore, the declaration was thoroughly reviewed but was found unpersuasive as it could not be determined from the disclosure as to which sequences of SEQ ID NOS 1-10 achieved the result shown in the declaration.

With regard to the traversal of Hogan, the rejection was made with regard to the Holmes reference. The Hogan reference was cited to show the high state of the art at the time of the invention with regard to aligning sequences from different closely related species and using regions of similarity and differences to design probes and primers to achieve detection of specific species.

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New Grounds of Rejection

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 7, 9-17, and 22-26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The recitation of "a nucleic acid molecule" reads on a product of nature. This rejection can be overcome by the recitation of "an isolated nucleic acid molecule".

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 7, 9-21 and newly added claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Firstly, it is unclear from the recitation in the claim whether the nucleic acids in question can possess a sequence of more than one of the specific SEQ ID NOS recited in the claims.

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Furthermore, the amendment to claim 7 encompasses any nucleic acid sequence comprising a sequence that is shorter than SEQ ID NO 1-10 (the recitation of "the sequence region comprising or being a phylogenetically conserved base sequence... wherein in a region of at least 10 successive nucleotides... it is 100% or at least 80% identical to a corresponding number of successive nucleotides of one or more of the following sequences...") or to sequences that are larger than SEQ ID NOS 1-10. The claim as amended thus reads on a sequence "comprising" (open terminology) a shortened sequence compared to SEQ ID NO 1-10. In other words, any sequence that is larger than SEQ ID NOS 1-10, are encompassed by the claims as presently amended. With respect to claim 9, the claim reads even more broadly on sequences that are larger than SEQ ID NOS 1-10, wherein the nucleic acid need only possess 8 or 9 out of 10 successive nucleotides of the nucleic acid sequence encompassed by claim 7. The claims are further drawn to methods of using such nucleic acids as well as kits comprising such nucleic acids. The specification, however, only teaches the specific nucleic acid sequences of SEQ ID NOS 1-10. The claimed sequences, however, read on a large number of sequences that will detect specific subspecies of *Salmonella*. With respect to claim 13, the claims read on any sequence such that 20% of it's nucleotides can be modified in each string of 10 successive nucleotides. Such a claim would read on a sequence only having 60% complementarity to SEQ ID NOS 1-10.

Furthermore, amendment of claim 7 to -a nucleic acid *consisting of*...-, while overcoming the rejection with respect to claim 7, does not overcome the rejection with respect to claim 9 as the claim would still read on a broad genus of sequences that have not been described in the

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specification. For example, the molecule of SEQ ID NO 1 consists of 20 nucleotides. Part (ii) of claim 5, however, stipulates that a nucleic acid molecule need only possess 9 out of 10 successive nucleotides of SEQ ID NO 1. Such a molecule could differ from SEQ ID NO 1 in 11 out of 20 positions, thus encompassing a molecule which could read on a probe or primer for a large number of other genes or sequences, from any species of *Salmonella*, which have not been described in the specification. The same analysis holds for part (iii) of claim 5.

Furthermore claim 9 recites "a nucleic acid which is homologous to a nucleic acid according to claim 7..." It is noted that applicants have listed a sequence which is known in the prior art and which is homologous to the claimed sequence. Absent factual evidence, a percentage sequence similarity of less than 100% is not deemed reasonable to support one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence homology results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule and therefore lacks support regarding written description.

The claimed invention represents a broad genus for which a representative number of species of such a genus must be disclosed to fulfill the description requirement of 112, first

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paragraph. As set forth by the Court in *Vas Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date, applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of the species of the isolated nucleic acids of SEQ ID NOS 1-10, or to methods of using such a broad genus of nucleotides, the specification fails to show that applicant was, in fact, "in possession of the claimed invention" at the time the application for patent was filed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 7, 9-17 and 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Holmes et al.

The claims are drawn to nucleic acids that comprise sequences of SEQ ID NOS 1-10 and methods of using such. Holmes teaches a sequence that comprises the sequence of SEQ ID NOS 1, 3, 6, and 9 of the instantly claimed invention.

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12. Claims 7, 9-13, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Olsen et al (US Patent 6,004,747).

Olsen teaches a sequence (Fig 1) which comprises the sequence of SEQ ID NOS 1, 3, 6, and 9 of the instantly claimed invention. Olsen teaches aligning sequences of different serovars of *Salmonella* to generate probes and primers for detection of the serovars of the instantly claimed invention (col 2-4). Olsen teaches kits comprising these probes and primers as well as methods of use. Furthermore, the claims of the Olsen patent encompass the claims of the instant invention (claim 1-19).

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600


Jehanne Souaya
Patent examiner

